Title: AntiCoagulation versus AcetylSalicylic Acid after Transcatheter Aortic Valve Implantation

ACASA-TAVI

AntiCoaulation vs AcetylSalicylic Acid after Transcatheter Aortic Valve Implantation

An investigator-sponsored prospective randomized open-label blinded-endpoint trial comparing the effect of anticoagulation treatment after transcatheter aortic valve implantation to the standard single anti-platelet treatment

Protocol v. ACASA-TAVI-2.2

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Protocol Synopsis

Sponsor	Oslo University Hospital
Phase and study type	Phase III, Prospective randomized open-label blinded endpoint (PROBE) trial
Investigational Medical Product (including active comparator and placebo) :	Direct oral anticoagulant-based antithrombotic treatment versus the standard acetylsalicylic acid-based antithrombotic treatment
Centres:	Oslo University Hospital, Rikshospitalet, Oslo, Norway
Study Period:	Estimated start September 1st, 2021 Anticipated recruitment duration 4 years until august 31st, 2025 Last subject last visit (end-of-trial): August 31st, 2026
Treatment Duration:	12 months
Follow-up:	12 months, 5 years, and 10 years

Objectives	The main goal of this study is to evaluate the effect and safety of direct oral anticoagulation versus versus acetylsalicylic acid after transcatheter aortic valve implantation
	
	Co-Primary endpoints 12 months:
	
	Hypo-attenuated leaflet thickening
	- CT evidence of increased hypo-attenuated leaflet thickness
	- Intention-to-treat, superiority, at 12 months
	
	Safety composite, composite of
	- VARC-3 bleeding events
	  - Type 1, 2, 3 or 4
	- Thromboembolic events
	  - Myocardial infarction

    - Stroke of any cause
- All-cause mortality
- Per-protocol, non-inferiority, at 12 months

Secondary endpoints at 12 months:

Key secondary endpoints (hierarchical):

- Clinical efficacy, intention-to-treat, superiority, composite of:
    - Freedom from all-cause mortality
    - Freedom from all stroke
    - Freedom from hospitalization for procedure- or valve-related causes
    - Freedom from KCCQ overall summary score <45 or decline from baseline of >10 points
- *Safety composite*, intention-to-treat, superiority
- Thromboembolic events
- Bleeding events
- All-cause mortality

Secondary safety endpoints:

- The number of adverse events
- The number of serious adverse events
- Life-threatening or disabling bleeding
- Major bleeding
- Minor bleeding

Exploratory secondary endpoints:

- CT signs of valve degeneration
- Echocardiographic signs of valve degeneration

- Non-procedure-related life-threatening or disabling bleeding (VARC-3)
- Number of major adverse clinical events, defined as stroke or transient ischemic attack of any cause, myocardial infarction, re-intervention on the aortic valve, death (cardiac, all-cause, non-cardiac) and heart failure hospitalization
- Quality of life as assessed by the KCCQ and the EQ5D 5L EuroQoL questionnaires, and HADS
- Per-protocol primary efficacy endpoint sensitivity analysis
- Intention-to-treat primary safety endpoint sensitivity analysis
- Cognitive function as assessed by the Mini-cog
- N-terminal pro-B-type natriuretic peptide (change)
- Cardiac troponin T (change)
- Infective endocarditis

Primary endpoint 5 and 10 years

Rate of MACE, composite of

- Cardiac death
- Aortic valve re-intervention
- Stroke
- Myocardial infarction
- Heart failure hospitalization
- Major, life-threatening, or disabling bleeding

Secondary endpoints 5 and 10 years

- Individual components of primary composite
- Echocardiography
    - These 3rd and 4th repeated echocardiographic

assessments of the implanted valve provide information on progression of hemodynamic structural valve degeneration

- Clinical efficacy
- NYHA-class trajectory
- Cognitive function as assessed by the Mini-cog
- N-terminal pro-B-type natriuretic peptide (change)
- Cardiac troponin T (change)
- Infective endocarditis

Study Design:	Dual arm, open label, blinded endpoint, randomised, active controlled trial
Main Inclusion Criteria:	Successful trans-catheter aortic valve implantation in patients aged >65 and <80 years old at the time of the procedure
Main Exclusion Criteria	Strict indication for anticoagulation or anti-platelet drugs Strict contraindication for anticoagulation or anti-platelet drugs Overt cognitive failure Failure to obtain written informed consent Concomitant use of inducers or inhibitors of CYP3A4 or P-glycoprotein
Sample Size:	360 patients
Efficacy Assessments:	Cardiac CT, echocardiography, clinical assessment
Safety Assessments:	Patient interview at 3, 6 and 9 months. Physical examination and clinical assessment after 12months.

Abbreviations

AS – aortic stenosis

ASA – acetylsalicylic acid

BARC – bleeding academic research consortium consensus

CT – computed tomography

DOAC – direct oral anti-coagulation

eCRF – electronic case report form

HALT – hypo-attenuated leaflet thickening

SmPC – summary of product characteristics

SVD – structural valve degeneration

TAVI – transcatheter aortic valve intervention

TIA – transient ischemic attack

VARC 3 – valve academic research consortium-3 consensus

Disclosures

The authors have no commercial interests or economic disclosures related to the project.

Background and rationale

Aortic stenosis is a highly prevalent valvular disease and an important cause of morbidity and mortality in the elderly population. Transcatheter aortic valve implantation (TAVI) is an effective intervention in patients with severe aortic stenosis and low surgical risk[1, 2]. The procedure is highly effective, safe, and widely implemented. Current recommendations support transcatheter treatment of younger patients, including patients from 65 years of age with low surgical risk[3, 4]. This practice increases the importance of long-term valve maintenance.

Observational data have suggested that early signs of valve degeneration are associated with an increased risk of embolic events[5, 6]. Because both ischemic and bleeding complications after TAVI can be life-threatening, it is important to establish the optimal anti-thrombotic treatment regime. Use of oral anticoagulation after implantation for bioprosthetic valves have been associated with resolved valve degeneration and possible favourable clinical effects[5, 6].

The current practice guidelines recommend that oral anticoagulation may be considered for 3 months after open surgical bioprosthetic valve implantation[7]. Patients with an independent indication for oral anticoagulation (i.e. atrial fibrillation or venous thromboembolism) are recommended to continue this treatment lifelong, but there is no recommendation for oral anticoagulation following TAVI in patients without other indications. In patients without indication for oral anticoagulation, the use of double anti-platelet therapy for 3-6 months following TAVI is recommended[7]. However, single anti-platelet therapy with acetylsalicylic acid (ASA) without clopidogrel has been reported to improve bleeding outcomes and a composite of bleeding and ischemic outcomes[8]. The effect of on oral anticoagulation-based treatment strategy compared to the standard single anti-platelet treatment strategy for valve maintenance after TAVI is unknown. The ongoing ATLANTIS trial (clinicaltrials.gov NCT02664649) is the only other trial assessing DOAC after TAVI. ATLANTIS trial is not powered for valve degeneration, does not include systematic imaging, is not powered for the subgroup of patients without indication for anticoagulation (and thereby also not powered for the comparison of DOAC vs single antiplatelet therapy), does not have blinded endpoint design, and includes an older population[9].

Increased anti-thrombotic treatment intensity may come at the cost of increased bleeding risk. Dual anti-platelet therapy and combination therapy with anticoagulation and anti-platelet therapy have both been associated with unfavourable outcomes[8, 10, 11]. Combined anti-platelet and anti-coagulation treatment has been shown to reduce valve degeneration at the cost of increased bleeding[12, 13]. Conversely, single anti-platelet therapy and anti-coagulation with a direct oral anti-coagulant (DOAC) have been associated with similar bleeding risk[14]. Bleeding rates in patients

treated with anti-coagulation after TAVI have been reported to be slightly higher than in patients treated with ASA after TAVI[8, 10], but patients with conventional indications for anti-coagulation have higher baseline bleeding risk than those without such indications. Therefore, the risk of bleeding in patients treated with DOAC or ASA following TAVI may be similar, but no randomized trials have been performed.

Objective

The primary objective is to evaluate the efficacy and safety of direct oral anticoagulation (DOAC) monotherapy versus acetylsalicylic acid (ASA) monotherapy after transcatheter aortic valve implantation.

Hypothesis

A DOAC-based strategy is superior to an ASA-based strategy to prevent valve degeneration in patients after successful TAVI, and non-inferior to ASA for safety. This advantage translates into favourable long-term clinical outcome.

Study endpoints

Study endpoints will comply with the updated endpoint definitions for aortic valve clinical research in VARC-3[15].

Co-primary endpoints at 12 months

The first objective of ACASA-TAVI is to assess whether DOAC can reduce the prevalence of valve degeneration after TAVI without imposing worse short-term clinical outcome. This study question translates to two co-primary endpoints, where both null hypotheses must be rejected for the intervention to be considered successful:

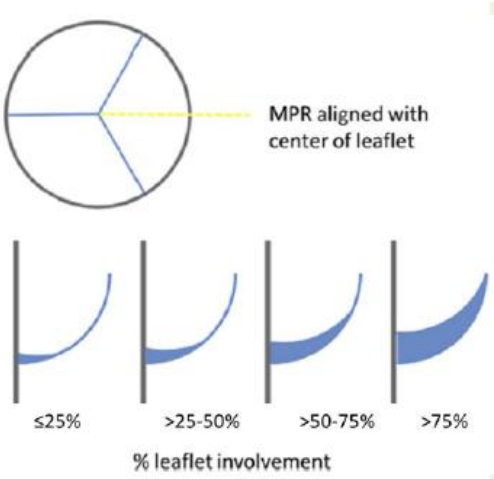


Figure 1 - Hypo-attenuated leaflet thickening. VARC-3, Eur Heart J 2021 00, 1-31

Hypo-attenuated leaflet thickening (HALT, first co-primary endpoint)

- Hypo-attenuated leaflet thickening (Figure 1)
- intention-to-treat, superiority, at 12 months

The first co-primary composite study endpoint is "*Hypo-attenuated leaflet thickening*" (hereafter "HALT"). The definition of *HALT* in ACASA-TAVI will be the rate of patients with at least one prosthetic leaflet with hypo-attenuated leaflet thickening (HALT) by cardiac CT as defined by VARC-3[15].

HALT is visually identified increased thickness of the bioprosthetic leaflet on the contrast-enhanced CT (see *Assessments*). This thickening typically extends from the stent frame leaflet origin and tapers towards the valve center. Reduced leaflet motion (RLM) was the primary endpoint of the GALILEO-4D trial[13], but it is now recommended to focus on HALT in clinical studies because RLM is subject to technical artifacts[15].

Management of valve degeneration observed at 12 months

Observation of HALT at 12 months can be expected in approximately 20% in the ASA-group, and fewer in the DOAC-group. There is currently no scientific indication that SVD Stage 1 represents a clinical problem. That question will be further addressed in the 5- and 10-year follow-up. Therefore, isolated SVD Stage 1 will not be managed clinically. In patients where a thrombus and/or hemodynamic bioprosthetic valve deterioration (Stage 2 or 3) is observed, clinical management will be initiated. This may include a course of DOAC. This will be registered in the eCRF.

Safety Composite (second co-primary endpoint)

- VARC-3 bleeding events
    - Type 1, 2, 3 or 4
- Thromboembolic events
    - Myocardial infarction
    - Stroke from any cause
- Death from any cause
- Per-protocol, *non-inferiority*, at 12 months

The second co-primary study endpoint is *Safety Composite* at 12 months. The rationale for this endpoint composition is the acknowledgement that reduction in valve degeneration is only of clinical value if the intervention does not worsen clinical outcome. Two main concerns are addressed:

- Will the use of DOAC increase bleeding risk?

- Will the omittance of ASA increase risk of stroke or myocardial infarction?

This clinical endpoint includes bleeding events according to the Valve Academic Research Consortium 3 (VARC-3) criteria[15] and thromboembolic events. Contrary to a common assumption, the current literature does not suggest that there will be a major difference in bleeding propensity between patients randomized to ASA or DOAC[14].

Thromboembolic events will include: Stroke of any cause and myocardial infarction. The inclusion of thromboembolic events in this non-inferiority endpoint is not straight forward. On one hand, some could argue that DOAC provides stronger protection against thromboembolic events than ASA, and therefore could bias a strict safety-endpoint towards non-inferiority. On the other hand, other clinicians are reluctant to omit ASA from the anti-thrombotic regime for safety concerns, similar to guideline practice after percutaneous coronary intervention. Therefore, the rationale for the non-inferiority endpoint is justified from a clinical standpoint. *Safety Composite* will also include death to ensure that important events are not missed by the composite. It is suggested by the VARC-3 consensus that mortality should primarily be assessed as all-cause mortality, and not limited to death from cardiac causes[15]. It will not include venous thromboembolism, because this would likely bias towards non-inferiority.

The clinical applicability compromise is to assess non-inferiority for *Safety Composite* of the DOAC-intervention to the active comparator. It is critical that bleeding events are registered without knowledge of study drug allocation. Therefore, data will be recorded on the outcome form via medical records and patient interviews before adjudication is made by the adjudication committee.

Secondary endpoints

Secondary endpoints are categorized as key secondary endpoints (hierarchical testing only), secondary safety endpoints (all tested for safety transparency) and exploratory secondary endpoints (all tested for hypothesis generation).

Key secondary endpoints (hierarchical)

- Clinical efficacy, intention-to-treat, superiority, composite of:
    - Freedom from all-cause mortality
    - Freedom from all stroke
    - Freedom from hospitalization for procedure- or valve-related causes

  - Freedom from KCCQ overall summary score <45 or decline from baseline of >10 points

- *Safety composite (second co-primary endpoint)*, intention-to-treat, superiority
- Thromboembolic events (stroke or myocardial infarction)
- Bleeding events (VARC-3 type 1, 2, 3 or 4)
- All-cause mortality
  - Sub-classified report of cardiovascular and non-cardiovascular mortality (see Assessments; Death)

Secondary safety endpoints

- The number of adverse events
- The number of serious adverse events
- Lethal bleeding (VARC-3 type 4) (Suspected or confirmed
- Life-threatening or disabling bleeding (VARC-3 type 3)
- Major bleeding (VARC-3 type 2)
- Minor bleeding (VARC-3 type 1)

Exploratory secondary endpoints

- Biosprosthetic valve deterioration Stage 1, 2 or 3
- CT signs of valve degeneration
  - Hypo-attenuated leaflet thickening by grade at patient level and leaflet level
  - Reduced leaflet opening classified by grade at patient level and leaflet level with and without hypo-attenuated leaflet thickening
  - Leaflet sclerosis
  - Leaflet calcification
  - Valve thrombosis
- Echocardiographic signs of valve degeneration
  - Delta value for mean gradient and estimated aortic valve opening area

  - Delta value for left ventricular ejection fraction
  - Valvular regurgitation grade delta value
- Non-procedure-related type 3 bleeding (VARC-3)
- Number of major adverse clinical events, defined as stroke or transient ischemic attack of any cause, myocardial infarction, re-intervention on the aortic valve, death (cardiac, all-cause, non-cardiac) and heart failure hospitalization
- Quality of life as assessed by the KCCQ and the EQ 5D 3L EuroQoL questionnaires, and HADS
- Patient-reported outcome
  - Favourable, acceptable or unfavourable according to VARC-3[15].
- Per-protocol primary efficacy endpoint sensitivity analysis
- Intention-to-treat primary safety endpoint sensitivity analysis
- Cognitive function as assessed by the Mini-cog
- N-terminal pro-B-type natriuretic peptide (change)
- Cardiac troponin T (change)
- Infective endocarditis

If other secondary endpoints become of interest during the study period, they will be highlighted as not pre-defined, and they will comply with the VARC-recommendations at the time.

Definitions

Bioprosthetic valve deterioration

BVD will be defined according to VARC-3[15].

- Stage 1
  - Hypo-attenuated leaflet thickening (HALT) with or without reduced leaflet motion (RLM) and no new hemodynamic abnormality (mean gradient <20 mmHg and valvular regurgitation less than moderate)
- Stage 2
  - Increased mean transvalvular gradient ≥10 mmHg resulting in ≥20 mmHg mean gradient with concomitant decrease in EOA ≥0.3cm^2 or ≥25%

  - Decrease in Doppler velocity index ≥0.1 or ≥20% compared with 3 month-control
  - New occurrence or increase of ≥1 grade of intraprosthetic regurgitation resulting in ≥ moderate aortic valve regurgitation

- Stage 3
  - Increased mean transvalvular gradient ≥20 mmHg resulting in ≥30 mmHg mean gradient with concomitant decrease in EOA ≥0.6cm^2 or ≥50%
  - Decrease in Doppler velocity index ≥0.2 or ≥40% compared with 3 month-control
  - New occurrence or increase of ≥2 grade of intraprosthetic regurgitation resulting in severe aortic valve regurgitation

The stages of bioprosthetic valve deterioration (BVD) are based on structural and functional characteristics of the valve, and not on patient response data, symptoms, or need for re-intervention. However, patients with symptoms attributable to SVD are likely to be identified by these criteria. Antithrombotic medication is also administered in patients after TAVI to lower the risk of systemic embolism (stroke or transient ischemic attack [TIA]), and these symptoms will not necessarily be captured by the SVD definition. Stroke or TIA will be registered at 12 months by the use of a dedicated blinded endpoint eCRF filled in by a study nurse via access to the medical records and patient interviews and adjudicated by the adjudication committee.

Endocarditis

Meeting at least one of the following criteria:

- Fulfilment of the Duke endocarditis criteria
- Evidence of abscess, pus or vegetation secondary to infection confirmed by histological or microbiological studies during surgery
- Evidence of abscess, pus or vegetation by autopsy

Corresponding objectives and endpoints at 12 months

	Objective	**Endpoint**
Primary	To assess whether DOAC treatment can reduce early valve degeneration after TAVI without risk of worse short-term clinical outcome compared to ASA treatment.	*First co-primary endpoint** - *HALT* (hypo-attenuated leaflet thickening) on cardiac CT, intention-to-treat, superiority *Second co-primary endpoint** - *Safety Composite* (Composite of: bleeding events, thromboembolic events, all-cause mortality), per protocol, non-inferiority

	The long-term clinical benefit will subsequently be assessed during long-time follow-up.	*both primary endpoints must be met for the trial to declare success
Secondary	To assess key signals of favourable effects of DOAC treatment compared to ASA treatment after TAVI.	*Key secondary endpoints (hierarchical):* - *Clinical efficacy* (Composite of: freedom from all-cause mortality, freedom from all stroke, freedom from hospitalization for procedure- or valve-related causes, freedom from KCCQ overall summary score <45 or decline from baseline of >10 points), intention-to-treat, superiority - *Safety Composite (second co-primary endpoint)*, intention-to-treat, superiority - Thromboembolic events, intention-to-treat, superiority - Bleeding events, intention-to-treat, superiority - All-cause mortality, intention-to-treat, superiority
Safety	To assess the safety profile of DOAC treatment after TAVI, compared to ASA treatment	*Secondary safety endpoints:* - The number of adverse events, safety population - The number of serious adverse events, safety population - Life-threatening or disabling bleeding, safety population - Major bleeding, safety population - Minor bleeding, safety population
Exploratory	To generate hypotheses of potential beneficial effects of DOAC treatment compared to ASA treatment after TAVI	*Exploratory secondary endpoints:* - CT signs of valve degeneration - Echocardiographic signs of valve degeneration - Non-procedure-related life-threatening or disabling bleeding (VARC-3) - Number of major adverse clinical events, defined as stroke or transient ischemic attack of any cause, myocardial infarction, re-intervention on the aortic valve, death (cardiac, all-cause, non-cardiac) and heart failure hospitalization - Quality of life as assessed by the KCCQ and the EQ5D 5L EuroQoL questionnaires, and HADS - Per-protocol primary efficacy endpoint sensitivity analysis - Intention-to-treat primary safety endpoint sensitivity analysis - Cognitive function as assessed by the Mini-cog - N-terminal pro-B-type natriuretic peptide (change) - Cardiac troponin T (change) - Infective endocarditis

Primary endpoint at 5 and 10 years

The important second objective of ACASA-TAVI is to assess whether a DOAC-based antithrombotic regime improves clinical outcome at intermediate and long-term follow-up. This translates into one composite primary outcome to be assessed at 5 years and 10 years.

Major adverse cardiac events (MACE)

Avoidance of major adverse cardiac events (MACE) is of great importance for the patient after a medical intervention. The primary endpoint is the rate of MACE at the 5- and 10-year milestone. We define MACE as a composite of one of the following:

- Cardiac death
- Heart failure hospitalization
- Re-intervention with valve-in-valve TAVI
- Stroke
- Myocardial infarction
- VARC-3 type 2 – 4 secondary to or exacerbated by antithrombotic treatment

The occurrence, number and time from TAVI till occurrence of these events will be registered by a study nurse or research fellow at 5 and 10 years and adjudicated in the eCRF by a blinded investigator.

Secondary endpoints at 5 and 10 years

These secondary endpoints will be exploratory of nature but will provide important information on the value of the DOAC intervention.

- Components of the composite endpoint
    - Cardiac death
    - Heart failure hospitalization
    - Re-intervention on aortic valve
    - Stroke
    - Myocardial infarction
    - VARC-3 type 2 – 4 secondary to or exacerbated by antithrombotic treatment

- Freedom from bioprosthetic valve failure
    - Defined as Valve-related mortality OR re-intervention on aortic valve OR BVD Stage 3
- Echocardiography
    - These 3rd and 4th repeated echocardiographic assessments of the implanted valve provide information on progression of hemodynamic structural valve degeneration
- Clinical benefit
    - NYHA-class trajectory
    - Cognitive function as assessed by the Mini-cog
    - N-terminal pro-B-type natriuretic peptide (change)
    - Cardiac troponin T (change)
    - Infective endocarditis

We will also assess whether an improvement in MACE was mediated by reduction in SVD at 12 months.

Study design

ACASA-TAVI is an investigator sponsored randomized controlled trial of prospective randomized open-label blinded-endpoint (PROBE) design.

Population

Patients aged less than 80 years at the time of the procedure who are accepted for TAVI by the heart team in a high-volume centre (Oslo University Hospital) are eligible for participation in the trial. All patients who receive TAVI in the study period will be screened for inclusion and approached on day one following successful TAVI. Patients will be included in the study only when written informed consent is provided.

Baseline characteristics, including age, sex and body-mass index, will be recorded. Comorbidities will be recorded with special attention to coronary artery disease, hypertension, diabetes mellitus, heart failure, previous stroke, peripheral artery disease, venous thromboembolism, chronic obstructive pulmonary disease or permanent pacemaker. Baseline glomerular filtration rate, cardiac troponin t

and NT-proBNP will be recorded. In addition, biobank samples will be obtained and frozen according to appropriate procedures.

Procedural characteristics will be recorded. The valve type and size will be noted, as well as valve-in-valve procedure and post-implantation dilation. The presence of supra-annular leaflet position will be noted, together with any procedural bleeding or thrombotic complications.

Inclusion criteria

All patients undergoing TAVI during the study period will be screened. Eligible patients:

- Patients aged >65 and <80 years old after successful TAVI
    - Successful TAVI will be defined as:
        - Freedom from mortality
        - Successful access, device delivery, and retrieval of the delivery system
        - Correct positioning of a single prosthetic heart valve into the proper anatomical location
        - No procedural complications or device related interventions that prevents the introduction of a study medication within 72 hours (ongoing uncontrolled bleeding, peripheral stent graft demanding antiplatelet drugs, coronary intervention, major stroke with risk of haemorrhagic transformation etc.)
- Signed informed consent and expected compliance with protocol

Successful TAVI will be defined as a procedure with successful deployment of a transcatheter valve without major vascular complication, stroke or myocardial infarction.

Exclusion criteria

It is an explicit aim of the study to assess a real-world population, and therefore exclusions criteria are established to reflect clinical practice. Patients will not be included if they have:

- Contraindication for DOAC or ASA
- Conventional indication for long-term DOAC
    - Atrial fibrillation
    - Recent or recurrent venous thromboembolism

  - Other

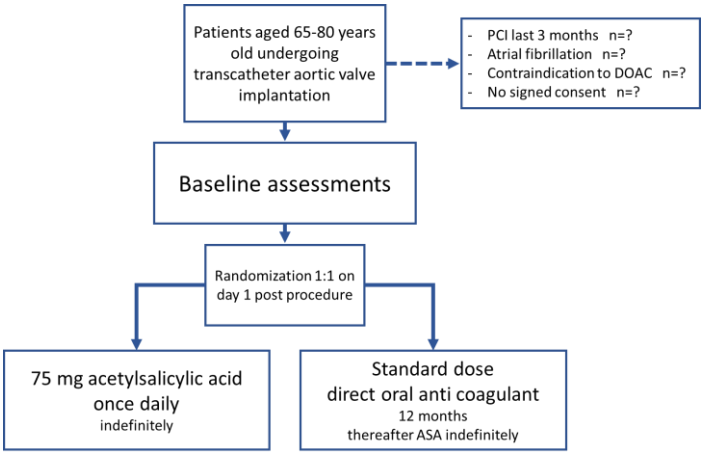
- Conventional indication for anti-platelet therapy
  - Recent percutaneous coronary intervention for chronic coronary syndrome (last 12 months)
  - Other
- Are unable to start the study medication within 72 hours after the procedure
- Concomitant use of inhibitors of CYP3A4 and P-glycoprotein (such as the antimycotic agents ketoconazole, itraconazole, voriconazole, posaconazole and HIV-protease inhibitors) and inducers of CYP3A4 and P-glycoprotein (phenytoin, carbamazepine, phenobarbital or St. Johns wort).

Management of patients meeting exclusion criteria

Patients who have provided signed consent in which screening reveals one or more exclusion criteria will be considered for inclusion in a parallel observational database in which no study related assessments are performed. These patients will be managed according to guideline recommendations, and the data from clinical follow-up will be registered.

Estimated study period

Oslo University Hospital, Rikshospitalet, performs approximately 500 TAVI procedures per year, and this figure is steadily increasing. We retrospectively assessed study inclusion and exclusion criteria in the patient population of 3 months from September to November 2020 prior to performing these calculations and observed that 43 of 72 patients (60%) would have been eligible for inclusion. This implies a realistic eligibility of approximately 100-120 patients per year. With an expanding number of procedures and some unwilling to participate, it seems reasonable to infer that inclusion of the 360 patients will be completed within 4 years. The analysis will therefore be performed 5 years after study start. With estimated inclusion start on September 1st 2021 we



estimate complete recruitment by August 31st 2025 and last subject last visit (LSLV) by August 31st 2026.

The time of LSLV will be the end-of-trial.

Five-year analysis will be performed after August 31st 2030, and ten-year analysis after August 31st 2035. The data will be destroyed five years after the concluding publication.

Management of low inclusion rate

Every patient undergoing TAVI in our unit will be assessed for screening. If the average quarterly inclusion rate falls below 23 (the number needed to include 360 in 4 years) we will approach collaborating units in Haukeland and Ullevål Hospitals to widen the inclusion.

Intervention

Participants will be randomized on day one post successful TAVI to antithrombotic treatment with either DOAC of anti Xa-type for 1 year followed by ASA indefinitely (intervention) or ASA indefinitely (control).

Treatment

Acetylsalicylic acid

The control group will receive ASA, the standard of care. The antiplatelet effect of ASA is due to its inhibition of cyclooxygenase. The standard dosing is 75 mg QD, and there are no dose adjustments.

The medication will be managed in agreement with the SmPC (Appendix).

If patients randomized to ASA strategy do not tolerate the drug, either due to adverse effects or unexpected allergy, conversion to clopidogrel is recommended according to current clinical practice. The treatment will be started immediately after randomization and will continue indefinitely.

In cases of ASA intolerance, conversion to clopidogrel, an inhibitor of ADP connection to the $P2Y_{12}$-receptor, will be considered. All reference safety information will be based on the SmPC for ASA.

Direct oral anticoagulant

The intervention group will receive an anti-Xa type DOAC (apixaban, rivaroxaban or edoxaban). DOAC of direct thrombin inhibition type (dabigatran) will be avoided to obtain homogenous intervention mechanisms and reduce concerns related to previous experience with surgical mechanical valves[16]. DOAC agents will be tested as monotherapies. This includes rivaroxaban which has previously been tested in combination with ASA[11]. Based on previous data from

patients with other clinical indications for DOAC treatment[10], it is unlikely that DOAC monotherapy will be inferior to standard therapy with ASA.

The choice of agent will be made after clinical discussion between the patient and the treating clinician, in which also possible pharmacological interactions or notes of cautions from the corresponding SmPC must be considered. The treatment will be started in a timely manner within 72 hours after randomization accommodating clinical judgement and any subsequent invasive procedures (like pacemaker implantation) and continue for 12 months. Thereafter, treatment will be converted to ASA indefinitely. One of the following agents will be used at the choice of the patient and clinician:

Apixaban

Apixaban is an anti-Xa type DOAC sold under the generic name “Eliquis”, and is the most widely used agent in our clinical practice. The standard dosing is 5 mg BID. This dose should be reduced to 2.5 mg BID if two or three of the following criteria are present:

- Age > 80 years (not relevant at inclusion in ACASA-TAVI but may occur during follow-up.
- Body weight < 60 kg
- Reduced renal function (Cl_{CR} 15-29 ml/min)

The medication will be managed in agreement with the SmPC (Appendix). All reference safety information will be based on the SmPC for apixaban.

Edoxaban

Edoxaban is an anti-Xa type DOAC sold under the generic name “Lixiana”. Standard dosing is 60 mg QD. This dose should be reduced to 30 mg QD if one of the following criteria are present:

- Reduced renal function (Cl_{CR} 15-50 ml/min)
- Low bodyweight ≤60 kg
- Use of the following P-gp-inhibitors: Ciclosporine, dronedarone, erythromycin or ketoconazole.

The medication will be managed in agreement with the SmPC (Appendix). All reference safety information will be based on the SmPC for edoxaban.

Rivaroxaban

Rivaroxaban is an anti-Xa type DOAC sold under the generic name “Xarelto”. The standard dosing is 20 mg QD. This dose should be reduced to 15 mg QD if the patient has reduced renal function (Cl_{CR} 15-49 ml/min).

The medication will be managed in agreement with the SmPC (Appendix). All reference safety information will be based on the SmPC for rivaroxaban.

Cost

Patients randomized to ASA will receive a refunded prescription based on the current approved treatment indication. Standard dose DOAC will cost approximately 9.000 NOK for one year treatment for one patient. The total cost of DOAC in ACASA-TAVI will be approximately 1.65 MNOK. Arrangements for supply of DOAC or financial re-imbursement of DOAC to patients allocated to the DOAC group are not finalized.

Duration

DOAC will be administered for 12 months. From the 12-month visit, all study participants will receive ASA 75 mg QD indefinitely.

Compliance

Participant compliance to the investigational products will be self-reported and registered at the 3-, 6-, 9- and 12-month visits. The data will be reported with the trial results. The batch numbers of used study medication will be registered at every time point.

Cross-over

If patients in the ASA-group develop an indication for anti-coagulation (i.e. atrial fibrillation or venous thromboembolism) during follow-up, they will cross over to the DOAC group. Conversely, patients in the DOAC-group who develop an indication for anti-platelet therapy (i.e. percutaneous coronary intervention) will cross over to the ASA-based group. The time of cross over will be noted.

Cross-over patients will remain in their original group for the intention-to-treat analyses, and per-protocol analyses will be performed as predefined.

Concomitant medication

Use of concomitant medication which is not a trial exclusion criterion (i.e. not a known inhibitor og inducer of CYP3A4 or P-glycoprotein) is permitted. Starting these medications during the trial period is not permitted. For other and permitted concomitant medication, potential interactions and notions of care from the SmPC shall be considered and noted at inclusion.

Consideration of placebo control

A traditional trial design to minimize bias is the double-blind placebo design. Placebo control was discussed during the planning of ACASA-TAVI. The study will assess a new intervention instead of, not in addition to, the old standard. The standard is dosed QD and the most common DOAC is BID. Production of identical pills containing one of the two agents would be costly. Adequately blinded adjudication of the pivotal study endpoints can be achieved using the PROBE-design. The primary endpoints and key secondary endpoints are not likely to be influenced by the lack of patient blinding. If anything, any reporting bias resulting from the lack of patient blinding could be expected to go in the direction of more bleeding reported in the DOAC group. This would bias the safety signal against DOAC, and a result suggesting agreeable safety would inspire more confidence.

After these thorough discussions we have decided that it is reasonable to utilize a PROBE-study design without patient blinding.

Study procedure

Study participants will be recruited from the group of patients undergoing TAVI for severe aortic stenosis at Oslo University Hospital. The age of all patients undergoing TAVI will be assessed and those aged less than 80 years old will be approached for further evaluation.

Screening

Informed consent

Voluntary, written informed consent (Appendix A) must have been obtained for each subject before any study specific procedure is initiated. At this time, the patient will be registered in the eCRF, and a unique identifier will be assigned.

The following tests will be performed at screening:

Physical examination

A physical examination (including examination of heart, lungs, abdomen, neck and assessment of peripheral circulation and oedema) must be performed; vital signs (blood pressure, and heart rate); and height and weight must be recorded.

Medical history

A medical history must be obtained, and age; gender; NYHA functional status; risk factors (hypertension, smoking, and diabetes mellitus); and concomitant disease must be recorded.

Quality of life

Self-reported, health-related quality of life will be gauged with the KCCQ and the EQ 5D 3L EuroQoL questionnaires, and HADS. We will allow subjects to complete the quality-of-life assessments before study procedures are performed.

Concomitant medication

All concomitant medication used by the participant within 28 days of the start of treatment must be recorded in the eCRF by generic name and dose.

Laboratory analyses

Fasting blood samples will be obtained to determine: Haemoglobin; white blood cell count, platelet count; serum potassium; serum sodium; glucose, glycosylated haemoglobin (HbA1c); creatinine; ALT; bilirubin; albumin; INR; CK; CRP; NT-proBNP; total cholesterol; LDL cholesterol, high density lipoprotein cholesterol and triglycerides. Blood for efficacy analyses (specified later) must be collected, drawn, and appropriately labelled and stored in a dedicated biobank for later analysis.

Echocardiography

A comprehensive echocardiographic exam for study purposes must be performed prior to study drug administration. A copy of this exam will be stored in the clinical imaging archive under the patient's real name for reasons of safety.

Quality of life

Self-reported, health-related quality of life will be gauged with the KCCQ and the EQ 5D 3L EuroQoL questionnaires, and HADS. We will allow subjects to complete the quality-of-life assessments before study procedures are performed.

Randomisation

After confirmation of eligibility, baseline measurements can be made, and the online randomisation process can be performed. If more than 72 hours have passed since the screening visit, the physical exam should be repeated, vital signs recorded anew, and safety blood samples should be repeated.

The project will utilize a secure eCFR with randomization tool (Viedoc®) for randomization of participants. After randomization, the caring cardiologist will enter a statement to the patient's electronic medical record declaring the allocation and treatment duration. This statement will be distributed to other physicians caring for the patients and will include a recommendation to only alter the study medication if it is critically important.

Study drug initiation

In patients randomized to DOAC, the treatment will be prescribed and initiated by the cardiologist attending to the patient on day 1 post TAVI. Antiplatelet drugs given prior to the procedure will be terminated.

In patients randomized to ASA, the treatment with 75 mg QD will be continued on day 1 post TAVI. Some patients will have received loading dose clopidogrel prior to TAVI. This drug will not be continued after inclusion.

Telephone contact or visit at 3, 6 and 9 months

These visits are for monitoring and assessing safety and adherence to protocol. Telephone contact will be the default, with an option to decide for physical visits according to the feasibility and convenience of the patient.

Subgroup assessment of patients from Sørlandet Hospital

Subgroup assessments at 3 months have been planned for all patients from one collaborating centre (Sørlandet Hospital). This subgroup analysis aims to assess the dynamics of early structural valve degeneration. No previous studies have reported the timing of onset of the first co-primary endpoint HALT, and this may give insights to the optimal DOAC treatment duration. This will be an exploratory subgroup assessment in which the standard clinical follow-up of echocardiography, medical history, physical exam and laboratory tests will be recorded and supplemented by a dedicated cardiac CT. The analysis will be performed after end-of-trial and the primary analysis, and the early effect of DOAC on valve dynamics and morphology will be reported.

Medical history

A medical history must be obtained, and NYHA functional status; well-being; adverse events; and concomitant disease must be recorded.

Concomitant medication

All concomitant medication used by the participant within 28 days of the start of treatment must be recorded in the eCRF by generic name and dose. Use of concomitant medication which is not a trial exclusion criterion (i.e. not a known inhibitor og inducer of CYP3A4 or P-glycoprotein) is permitted. Starting these medications during the trial period is not permitted. For other and permitted concomitant medication, potential interactions and notions of care from the SmPC shall be considered and noted at inclusion.

Safety assessment

Any untoward medical event (i.e. any AE, SAE or SUSAR) since the last visit must be recorded in the eCRF and the patient medical record.

Drug discontinuation

Discontinuation of the drug from the allocated study arm will be recorded together with the reason for the discontinuation. If a drug adverse effect in the DOAC group is the reason for discontinuation (i.e. nausea), transfer to another anti-Xa type DOAC will be considered and registered.

End of treatment visit

This study visit 12 months after TAVI assesses efficacy and safety.

Cardiac CT

A study purpose cardiac CT will be performed at 12 months after TAVI.

Echocardiography

A comprehensive echocardiographic exam for study purposes must be performed at the end of treatment. A copy of this exam will be stored in the clinical imaging archive under the patient's real name for reasons of safety.

Quality of life

Self-reported, health-related quality of life will be gauged with the KCCQ and the EQ 5D 3L EuroQoL questionnaires, and HADS. We will allow subjects to complete the quality-of-life assessments before study procedures are performed.

Medical history

A medical history must be repeated, and NYHA functional status; any change in risk factors (hypertension, smoking, diabetes mellitus), and concomitant disease must be recorded. Any medical events since inclusion in trial must be evaluated. Current well-being, symptoms, potential side effects and physical capacity must be assessed.

Physical examination

A physical examination must be performed, and results (including examination of heart, lungs, abdomen, neck and assessment of peripheral circulation and oedema); vital signs (blood pressure, and heart rate); and height and weight must be recorded.

Concomitant medication

All concomitant medication (incl. vitamins, herbal preparation and other “over-the-counter” drugs) used by the participant within 28 days of treatment start must be recorded in the eCRF by generic name and dose.

Laboratory analyses

Fasting blood samples will be obtained to determine: Haemoglobin; white blood cell count, platelet count; serum potassium; serum sodium; glucose, glycosylated haemoglobin (HbA1c); creatinine; ALT; bilirubin; albumin; INR; CK; CRP; TnT and NT-proBNP; total cholesterol; LDL cholesterol, high density lipoprotein cholesterol and triglycerides(safety). Blood for efficacy analyses must be collected, appropriately labelled and stored in a dedicated biobank for later analysis.

Safety assessment

Any untoward medical event (i.e. any AE, SAE or SUSAR) since the last visit must be recorded in the eCRF and the patient medical record.

5-year assessment

This visit 5 years after TAVI will assess efficacy.

Echocardiography

A comprehensive echocardiographic exam for study purposes must be performed at the end of treatment. A copy of this exam will be stored in the clinical imaging archive under the patient’s real name for reasons of safety.

Quality of life

Self-reported, health-related quality of life will be gauged with the KCCQ and the EQ 5D 3L EuroQoL questionnaires, and HADS. We will allow subjects to complete the quality-of-life assessments before study procedures are performed.

Medical history

A medical history must be repeated, and NYHA functional status; any change in risk factors (hypertension, smoking, diabetes mellitus), and concomitant disease must be recorded. Any medical events since inclusion in trial must be evaluated. Current well-being, symptoms, potential side effects and physical capacity must be assessed.

Physical examination

A physical examination must be performed, and results (including examination of heart, lungs, abdomen, neck and assessment of peripheral circulation and oedema); vital signs (blood pressure, and heart rate); and height and weight must be recorded.

Concomitant medication

All concomitant medication (incl. vitamins, herbal preparation and other “over-the-counter” drugs) used by the participant within 28 days of treatment start must be recorded in the eCRF by generic name and dose.

Laboratory analyses

Fasting blood samples will be obtained to determine: Haemoglobin; white blood cell count, platelet count; serum potassium; serum sodium; glucose, glycosylated haemoglobin (HbA1c); creatinine; ALT; bilirubin; albumin; INR; CK; CRP; TnT and NT-proBNP; total cholesterol; LDL cholesterol, high density lipoprotein cholesterol and triglycerides(safety).

10-year assessment

This visit 10 years after TAVI will assess efficacy.

Echocardiography

A comprehensive echocardiographic exam for study purposes must be performed at the end of treatment. A copy of this exam will be stored in the clinical imaging archive under the patient’s real name for reasons of safety.

Quality of life

Self-reported, health-related quality of life will be gauged with the KCCQ and the EQ 5D 3L EuroQoL questionnaires, and HADS. We will allow subjects to complete the quality-of-life assessments before study procedures are performed.

Medical history

A medical history must be repeated, and NYHA functional status; any change in risk factors (hypertension, smoking, diabetes mellitus), and concomitant disease must be recorded. Any medical events since inclusion in trial must be evaluated. Current well-being, symptoms, potential side effects and physical capacity must be assessed.

Physical examination

A physical examination must be performed, and results (including examination of heart, lungs, abdomen, neck and assessment of peripheral circulation and oedema); vital signs (blood pressure, and heart rate); and height and weight must be recorded.

Concomitant medication

All concomitant medication (incl. vitamins, herbal preparation and other “over-the-counter” drugs) used by the participant within 28 days of treatment start must be recorded in the eCRF by generic name and dose.

Laboratory analyses

Fasting blood samples will be obtained to determine: Haemoglobin; white blood cell count, platelet count; serum potassium; serum sodium; glucose, glycosylated haemoglobin (HbA1c); creatinine; ALT; bilirubin; albumin; INR; CK; CRP; TnT and NT-proBNP; total cholesterol; LDL cholesterol, high density lipoprotein cholesterol and triglycerides(safety).

Table summary

	Screening	Discharge	3 months	6 months	9 months	1 year	5 years	10 years
Study medication		Randomized after TAVI to DOAC or ASA for 12 months						
ASA treatment						ASA indefinitely from 1 year		
Echocardiography	X	X	X*			X	X	X
Carciac CT			X*			X		
Medical history	X		X	X	X	X	X	X
Physical exam	X	X	X*			X	X	X

AE/SAE/SUSAR		X	X	X	X	X		
Quality of life	X					X	X	X
Medication	X		X	X	X	X	X	X
Lab tests	X	X	X*			X	X	X

Subgrous assessments at Sørlandet Hospital are marked by *. Screening assessments occur before randomization. Assessments in green after randomization will be forwarded for blinded adjudication. Echocardiography will include assessment of LV function and quantification of valve performance. Cardiac CT will assess signs of structural valve degeneration. All concomitant medication will be recorded at every time point. Lab tests will include hematologic cell count and biochemistry including NT-proBNP and troponin T.

Patient discontinuation

Patients may be discontinued from study treatment and assessments at any time. Specific reasons for discontinuing a patient for this study are:

- Voluntary discontinuation: participating patients are free to discontinue his/her participation in the study at any point in time, without prejudice to further treatment.
- Major protocol deviation
- Incorrect randomisation, i.e. the patient does not meet the required inclusion/exclusion criteria for the study
- Patient lost to follow-up
- Patient's non-compliance to study treatment and/or procedures

Procedures for discontinuation

Study drug discontinuation

The study participants may discontinue study drug treatment at any time according to their preferences. The investigator may also advise study drug discontinuation in case of side effects, if adverse effects of the treatment are suspected, or if contraindications to the continued use of DOAC or ASA arise. Study drug discontinuation and the reason why must be documented in the eCRF as well as in the hospital record. Efforts should be made to make ensure that adherence to the study protocol is kept up even though the patient no longer takes the study drug. All available data will be used in the intention to treat analysis, unless the patient specifically disagrees to let the investigator use his or her data.

Patient discontinuation

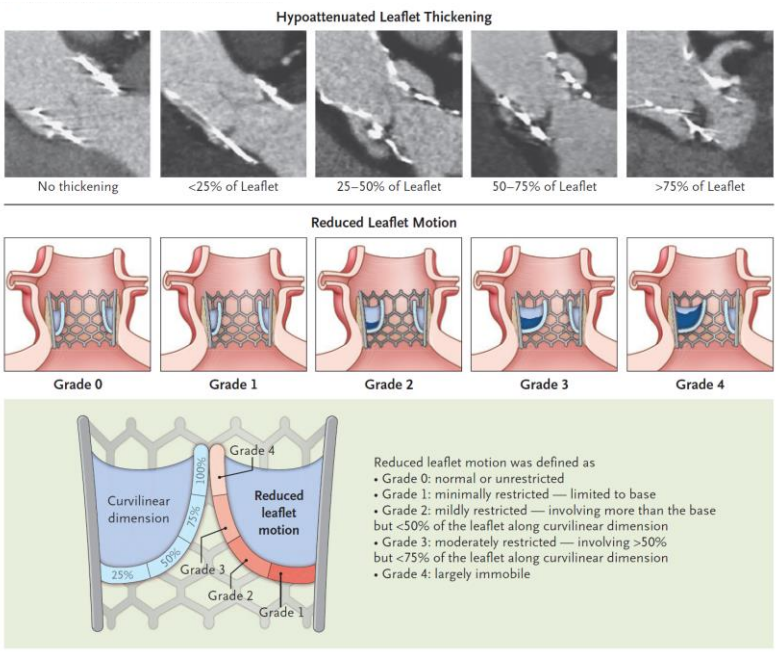
Patient withdrawal must be documented in the eCRF as well as in hospital records. If possible, a final assessment should be obtained (end of study visit). The reason for discontinuation is recorded. The investigator is obliged to follow up any significant adverse events until the outcome either is recovered or resolved, recovering/resolving, not recovered/not resolved, recovered/resolved with sequelae, fatal or unknown. Patients who withdraw will be included in the intention-to treat analysis.

Trial discontinuation

The whole trial may be discontinued at the discretion of the primary investigator or the sponsor in the event of any of the following:

- Occurrence of AEs unknown to date in respect of their nature, severity and duration
- Medical or ethical reasons affecting the continued performance of the trial
- Difficulties in the recruitment of patients

The sponsor and principal investigator will inform all investigators, the relevant Competent Authorities and Ethics Committees of the termination of the trial along with the reasons for such action. If the study is terminated early on grounds of safety, the Competent Authorities and Ethics Committees will be informed within 15 days.



Cardiac CT assessment of hypoattenuated leaftlet thickening and reduced leaflet motion. From De Backer O, Dangas GD, Jilaihawi H et al. Reduced Leaflet Motion after Transcatheter Aortic-Valve Replacement. NEJM 2020;382:130-139.

Assessments

Cardiac computed tomography

Cardiac imaging is well suited to assess valve function and structure. Especially, cardiac CT has been utilized to assess leaflet thickness and describe their mobility after TAVI[6, 12, 13]. Contrast-enhanced, ECG-gated cardiac CT with full

cardiac cycle coverage will be performed on pre-evaluated CT scanners ensuring the optimal image quality. Pilot sets will be assessed by the adjudication committee before study assessments are performed. CT scanners must be high-end with >64 detector technology, preferably 260-row multidetector scanners. Dedicated 4D CT volume image protocol will be used. Image noise will be defined at level 30. The majority of scans will be obtained at a single center. Vendors and models will be noted.

Patients will be pre-treated with betablocker or ivabradine to ensure heart rate below 65 bpm during acquisition. Typically, 50 to 150 mg metoprolol will be administered approximately 2 hours before the scan. Additional intravenous betablocker may be given to patients with heart rate above 60 bpm at scan start. Patients who do not tolerate betablockers will receive 15 mg ivabradine 2 hours before the scan. Local practice for contrast injection site and agent will be noted. Typically 70-110 ml of Visipaque (GE Healthcare) will be used. Arterial phase trigging covering the whole cardiac cycle is needed. Start and end positions of the scan will be defined by the initial scanogram. Start will be 20 mm cranial to the metal stent frame and the end will be 16 mm caudal. The resulting scan field must be at least 1 cm above and 1 cm below the TAVI stent frame. Images should be reconstructed at the lowest slice thickness at every 5% of the cardiac cycle. Radiation doses will be approximately 10 mSv per exam. Dose-modulation approach can be used (reduced dose in diastole).

Exams will be de-identified by a research nurse, research fellow or principal investigator and uploaded in DICOM format for analysis by an expert cardiologist who will perform all assessments blinded to the intervention. Valve leaflets will be assessed systematically by 2D and 3D volume-rendered imaging. 3D-RV images will be assessed as a cine-loop through the cardiac cycle to assess valve opening. Hypo-attenuated valve leaflet thickening and motion will be graded with multiplane reformats. Leaflet mobility is graded in agreement with previous trials utilizing this method[13]. The following parameters will be recorded

Hypo-attenuated leaflet thickening (HALT)

- Hypo-attenuating thickening in typically meniscal configuration on one or more leaflets visually identified on computed tomography (2D multiplanar reconstructions or 3D volume-rendering), with or without reduced leaflet motion (RLM)[d]
- The extent of HALT should be described per leaflet, using a 4-tier grading scale in regard to leaflet involvement along the curvilinear contour, assuming maximum involvement at the base of the leaflet:
  - ≤25% (limited to the base)
  - >25% and ≤50%
  - >50% and ≤75%
  - >75%
  - *Inconclusive for HALT:* imaging with insufficient image quality or presence of artifact

Reduced leaflet motion (RLM)

- Reduced leaflet excursion in the presence of HALT identified on computed tomography (2D multiplanar reconstructions or 3D volume rendering) and/or trans-oesophageal echocardiography
- The extent of RLM should be described per leaflet, using a 4-tier grading scale
  - *None:* no reduction in leaflet excursion
  - <50% reduction in leaflet excursion
  - ≥50% reduction in leaflet excursion
  - *Immobile:* immobile leaflet
  - *Inconclusive for RLM:* imaging with insufficient image quality or presence of artefact

Presentation

- *Subclinical:* Absent or mild haemodynamic changes and absent symptoms or sequela compatible with valve thrombosis or thromboembolism.
- *Clinically significant:* See *Table 15*

Timing

- *Acute:* Within 0–24 h of the index procedure
- *Subacute:* >24 h and ≤30 days after the index procedure
- *Late:* >30 days and ≤1 year after the index procedure
- *Very late:* >1 year after the index procedure

at 12 months:

- Hypo-attenuated leaflet thickening (Figure 1, upper panel)
    - Any thickening a leaflet visible on contrast-enhanced reconstructions with careful alignment of the long and short axes of the prosthesis will be registred
    - Any definite leaflet thickening will be defined as “leaflet thickening”
- Leaflet motion (Figure 1, lower panel)
    - Any restriction of leaflet mobility will be noted and graded
    - ≥ Grade 3 will be defined as “reduced leaflet motion”
- Leaflet calcification
- Leaflet sclerosis

One investigator will perform all analyses. The intra-observer variability will be reported in a randomly generated sample of 20 individuals.

Echocardiography

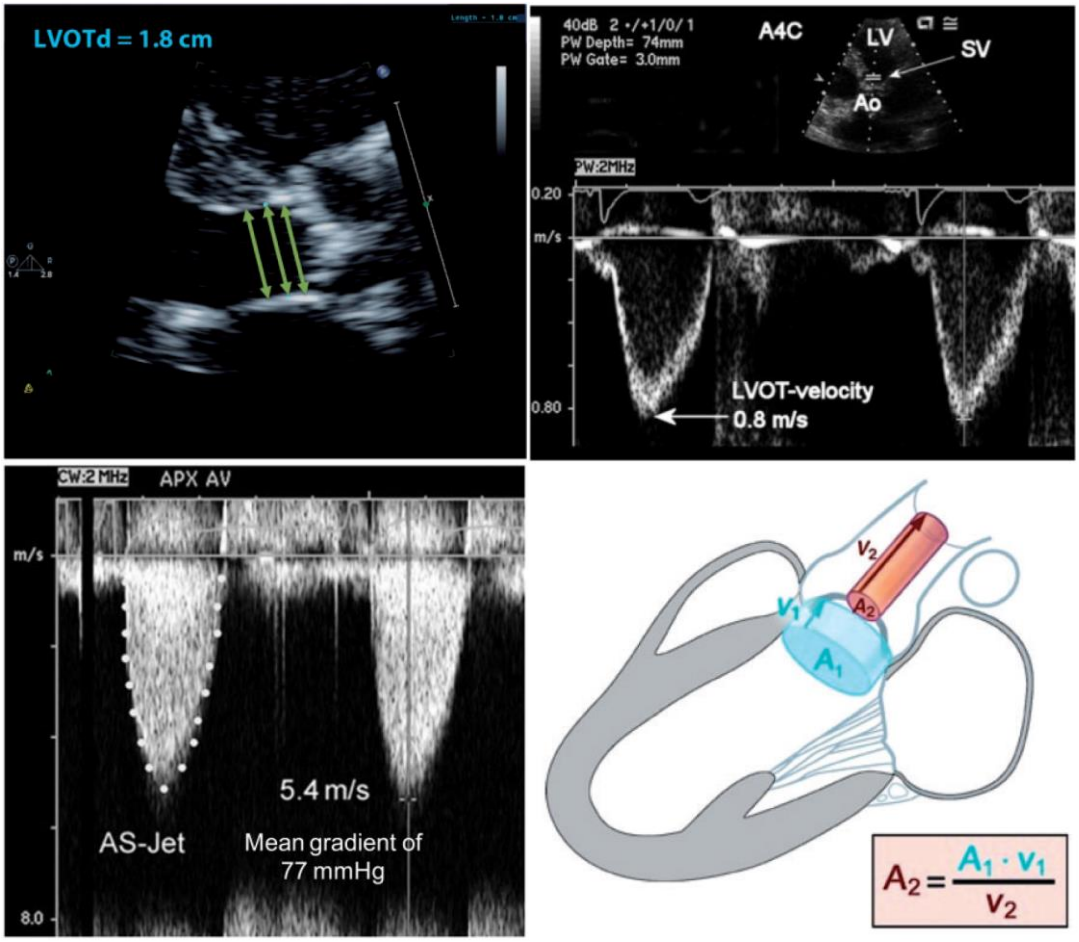
Echocardiography is the primary imaging modality for assessment of valvular function and is well suited to determine the degree of aortic stenosis[17]. Echocardiographic loops will be obtained on a Vivid E95 or newer scanner (GE Vingmed, Horten, Norway) with the patient in the left cubital position. A comprehensive baseline echocardiogram including all standard views will be obtained on day one after TAVI and again after 12 months by a dedicated echocardiography technician. Exams will be de-identified by a study nurse, research fellow or principal investigator and uploaded for analysis by a blinded expert cardiologist. The following echocardiographic parameters will be recorded before hospital discharge and at 12 months:

- Aortic valve mean gradient
- Aortic valve area
    - Based on measured left ventricular outflow tract dimensions
- Left ventricular ejection fraction by Simpson method from apical four-chamber and two-chamber views

- Global longitudinal strain by speckle tracking imaging from apical four-chamber, long-axis and two-chamber views using loops with more than 60 frames per second.
- Aortic valve regurgitation
    - Valvular or para-valvular
    - < moderate or ≥ moderate
- Para-valvular regurgitation

In addition to this, results from a comprehensive echocardiography performed shortly before TAVI will be included in the baseline characteristics:

- Aortic valve mean gradient
- Aortic valve area
- Left ventricular ejection fraction
- Left ventricular global longitudinal strain
- Presence of low-flow low-gradient
- Presence of non-tricuspid morphology



Estimation of aortic stenosis severity. From Baumgartner HC, Hung JC-C, et al. Recommendations on the echocardiographic assessment of aortic valve stenosis: a focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. European Heart Journal Cardiovascular Imaging. 2017;18:254-275.

Echocardiography will be repeated after five years and ten years to assess the trajectory of myocardial function and valve hemodynamics.

One investigator will perform all analyses. The intra-observer variability will be reported in a randomly generated sample of 20 individuals.

Transoesophageal echocardiography

One in eight randomly selected (stratified from each intervention group) patients will be invited to participate in a sub-study where the precision of transoesophageal echocardiography (TEE) to identify SVD stage 1 will be assessed. Cardiac CT is the gold standard, but the use of contrast and ionizing radiation is a challenge. Also, the availability of the cardiac CT can be a challenge. TEE may be an uncomfortable procedure, but complications are uncommon. Patients will be thoroughly

informed by the operator before the procedure. The images will be de-identified and read by an expert reader blinded to the intervention.

The TEE will be performed in right cubital position with standard pre-medication with 5 mg diazepam and 12.5 mg petidin. The ultrasonoscope will be connected to a Vivid E95 scanner (GE Vingmed). The procedure will be performed by a very experienced cardiologist, and will include a rapid and focused assessment of leaflet thickness and leaflet mobility 12 months after TAVI. The procedure will be interrupted at the patients wish.

Cerebral magnetic resonance imaging

One in eight randomly selected patients (stratified from each intervention group) will be invited to participate in a sub-study in which the prevalence and intervention effect on cerebral embolization will be assessed. Cerebral magnetic resonance (MR) will be performed on a dedicated 3T-scanner. The images will be de-identified and interpreted by an expert reader blinded to the intervention.

Clinical events

Relevant clinical events occurring after randomization will be registered at the time of the 12-month follow-up. These events will include:

- VARC-3 bleeding events
- Life-threatening or disabling events or major events with date
    - Minor bleeding (BARC 2 or 3a), non-procedure related
- Stroke of any cause, with date
- Myocardial infarction, with date
- Ischemia driven coronary vascularization, with date
- Pacemaker or implantable cardioverter defibrillation implantation
- Hospitalization for heart failure, with date
- Re-intervention, post-dilatation, surgical aortic valve replacement or valve-in-valve
- Death (any cause, cardiac non-cardiac), with date

Bleeding events

Bleeding events will be recorded at every time point. In cases of major, life-threatening or disabling bleeding, time to bleeding from TAVI will be registered.

Outcome definition:

- Life-threatening or disabling, major bleeding og minor bleeding according to VARC-3 definition

VARC-3 classification of bleeding complications of transcatheter aortic valve implantation

Overt bleeding[b] that fulfils one of the following criteria:

Type 1
- Overt bleeding that does not require surgical or percutaneous intervention, but does require medical intervention by a health care professional, leading to hospitalization, an increased level of care, or medical evaluation (BARC 2)
- Overt bleeding that requires a transfusion of 1 unit of whole blood/red blood cells[c] (BARC 3a)

Type 2
- Overt bleeding that requires a transfusion of 2–4 units of whole blood/red blood cells[c] (BARC 3a)
- Overt bleeding associated with a haemoglobin drop of >3 g/dL (>1.86 mmol/L) but <5 g/d (<3.1 mmol/L) (BARC 3a)

Type 3
- Overt bleeding in a critical organ, such as intracranial, intraspinal, intraocular, pericardial (associated with haemodynamic compromise/tamponade and necessitating intervention), or intramuscular with compartment syndrome (BARC 3b, BARC 3c)
- Overt bleeding causing hypovolemic shock or severe hypotension (systolic blood pressure <90 mmHg lasting >30 min and not responding to volume resuscitation) or requiring vasopressors or surgery (BARC 3b)
- Overt bleeding requiring reoperation, surgical exploration, or re-intervention for the purpose of controlling bleeding (BARC 3b, BARC 4)
- Post-thoracotomy chest tube output ≥2 L within a 24-h period (BARC 4)
- Overt bleeding requiring a transfusion of ≥5 units of whole blood/red blood cells (BARC 3a)[c]
- Overt bleeding associated with a haemoglobin drop ≥5 g/dL (≥3.1 mmol/L) (BARC 3b).

Type 4
- Overt bleeding leading to death. Should be classified as:
  - ***Probable:*** Clinical suspicion (BARC 5a)
  - ***Definite:*** Confirmed by autopsy or imaging (BARC 5b)

[a]The timing, indication, and number of transfused blood products should be collected and reported specifically during the index procedure, during the entire index hospitalization, and during follow-up after discharge, whether or not overt bleeding is identified.
[b]Overt bleeding is defined as any clinically obvious source of bleeding or bleeding source identified after appropriate investigation and diagnostic testing (e.g. imaging). Any procedural blood loss should be considered overt bleeding.
[c]Total number of transfusions should be reported separately for (i) within 48 h of the index procedure, (ii) the total duration of the index procedure hospitalization, and (iii) during any subsequent repeat hospitalization.

VARC-3 updated endpoint definitions for aortic stenosis, Eur Heart J 2021 00, 1-33

Stroke

Time to stroke will be recorded. Stroke will be defined as following:

- Acute episode of a focal or global neurological deficit with at least one of the following: change in the level of consciousness, hemiplegia, hemiparesis, numbness, or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke
- Stroke: duration of a focal or global neurological deficit > 24 h; OR < 24 h if available neuroimaging documents a new haemorrhage or infarct; OR the neurological deficit results in death
- No other readily identifiable non-stroke cause for the clinical presentation (e.g. brain tumour, trauma, infection, hypoglycaemia, peripheral lesion, pharmacological influences), to

be determined by or in conjunction with the designated neurologist. (Patients with non-focal global encephalopathy will not be reported as a stroke without unequivocal evidence of cerebral infarction-based upon neuroimaging studies)

- Confirmation of the diagnosis by at least one of the following:
    - Neurologist or neurosurgical specialist
    - Neuroimaging procedure (CT scan or brain MRI), but stroke may be diagnosed on clinical grounds alone

Stroke outcome definition

- Disabling stroke: a modified Rankin Scale (mRS) score of 2 or more at 90 days and an increase in at least one mRS category from pre-stroke baseline
- Non-disabling stroke: an mRS score of < 2 at 90 days or one that does not result in an increase of at least on mRS category from pre-stroke baseline

Stroke classification

- Ischemic: an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of the central nervous system tissue
- Haemorrhagic: an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid haemorrhage
- A stroke may be classified as undetermined if there is insufficient information to allow categorization as ischemic or haemorrhagic

Transient ischemic attack (TIA) will be recorded and defined as duration of a focal or global neurological deficit < 24 h, any variable neuroimaging does not demonstrate a new haemorrhage or infarct, but not be classified as a stroke.

Myocardial infarction

Time to myocardial infarction will be registered at every time point.

Peri-procedural MI

Myocardial infarction occurring within 72 hours after TAVI will be classified as peri-procedural MI if:

- New ischemic symptoms (e.g. chest pain or shortness of breath), or new ischemic signs (e.g. ventricular arrhythmias, new or worsening heart failure, new ST-segment changes,

hemodynamic instability, new pathological Q waves in at least two contiguous leads, imaging evidence of new loss of viable myocardium or new wall motion abnormality)

- Elevated cardiac biomarkers (preferable CK-MB) within 72 h after the index procedure, consisting of at least one sample post-procedure with a peak value exceeding 15 x as the upper reference limit for troponin or 5 x for CK-MB. If cardiac biomarkers are increased at baseline (>99th percentile), a further increase in at least 50% post-procedure is required
- the peak value must exceed 99th percentile

Spontaneous MI

Myocardial infarction occurring more than 72 h after TAVI will be classified as spontaneous MI if:

- Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile upper reference limit, together with the evidence of myocardial ischemia with at least one sign of ischemia:
    - New ischemic symptoms (e.g. chest pain or shortness of breath)
    - ECG changes indicative of new ischemia: new ST-T changes or new left bundle branch block (LBBB)
    - New pathological Q-waves in at least two contiguous leads
    - Imaging evidence of a new loss of viable myocardium or new wall motion abnormality
- Sudden, unexpected cardiac death occurring before blood samples could be obtained, or at a time before the detection of cardiac biomarkers in the blood, often with antecedent symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST elevation, or new LBBB, and/ or evidence of fresh thrombus by coronary angiography and/or at autopsy
- Pathological findings of an acute myocardial infarction

Death

Time to death will be recorded at every time point. Death will be classified as:

- Death due to immediate cardiac cause (e.g. myocardial infarction, cardiac tamponade, worsening heart failure)

- Death caused by non-coronary vascular conditions such as neurological events, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease
- All procedure-related deaths, including those related to a complication of TAVI or treatment for a complication of TAVI
- All valve-related deaths including SVD and other valve-related adverse events
- Sudden or unwitnessed death
- Death of unknown cause

Laboratory analyses

Blood samples will be obtained to determine: Hemoglobin, white blood cell count, platelet count, serum potassium; serum sodium; glucose, glycosylated hemoglobin (HbA1c); creatinine; ALT; bilirubin; albumin; INR; CRP; N-terminal pro-B-type natriuretic peptide (NT-proBNP); total cholesterol; ferritin; transferrin, serum iron and total iron binding capacity.

Extra blood will also be appropriately labelled and stored in a biobank and later analyzed for vasoactive peptides such as, ST2 and N-terminal pro-B-type natriuretic peptide. We will also assess markers of fibrosis, inflammation and relevant metabolic pathways.

Quality of life

Quality of life will be examined at baseline and at the end of the study using standard validated questionnaires; the EQ 5D 3L EuroQoL questionnaire, EQ-VAS, HADS and KCCQ questionnaires. The EQ 5D 3L EuroQoL questionnaire consists of 2 pages, the EQ-5D descriptive system and the EQ visual analogue scale. The Hospital Anxiety and Depression Scale (HADS) measures anxiety and depression symptoms. KCCQ is a commonly used 23 item self-administered questionnaire designed to evaluate physical limitations, symptoms (frequency, severity, and changes over time), social limitations, self-efficacy, and quality of life in patients with heart disease.

Cognitive function

Cognitive function will be assessed with the miniCog questionnaire. In this test the patient is challenged to remember three words and should be able to draw the time on a clock.

Safety monitoring and reporting

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an adverse event (AE) or serious adverse event (SAE). Each patient will be

instructed to contact the investigator immediately should they manifest any signs or symptoms they perceive as serious. When judging whether an adverse event is unexpected or not, the Summary of Product Characteristic (SmPC) for the study drugs apixaban, rivaroxaban and edoxaban will be used as reference safety information.

The methods for the collection of safety data are described below.

Definitions

Adverse event (AE)

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

The term AE is used to include both serious and non-serious AEs.

If an abnormal laboratory value/vital sign are associated with clinical signs and symptoms, the sign/symptom should be reported as an AE and the associated laboratory result/vital sign should be considered additional information that must be collected on the relevant eCRF.

Adverse events of special interest (AESI)

In general, AESIs are AEs that occur in categories of special interest with regard to determining the benefit/risk profile and overall safety of a drug. Previous data on antithrombotic treatment in atrial fibrillation have suggested that adverse events may be more common in the ASA-group than in the DOAC group (22% vs 27%)[14].

Unrecognized pregnancy or risk of pregnancy during the study period is a common area of special interest. This study will include elderly patients aged 65 to 80 years old, and we do therefore not consider unrecognized pregnancy to be a risk in this situation.

Serious adverse event (SAE)

Any untoward medical occurrence that:

- Results in death
- Is immediately life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation

- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the subject or may require medical intervention to prevent one of the outcomes listed above.

Medical and scientific judgment will be exercised in deciding on the seriousness of a case. Important medical events may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the listed outcomes in the definitions above. In such situations, or in doubtful cases, the case should be considered as serious. Hospitalisation for administrative reason (for observation or social reasons) is allowed at the investigator's discretion and will not qualify as serious unless there is an associated adverse event warranting hospitalisation.

Suspected unexpected serious adverse reaction (SUSAR)

Adverse Reaction: all untoward and unintended responses to an investigational medicinal product related to any dose administered.

Unexpected Adverse Reaction: an adverse reaction, the nature or severity of which is not consistent with the applicable product information.

Suspected Unexpected Serious Adverse Reaction: SAE (see above) that is unexpected and possibly related to the investigational medicinal products. When judging whether a possibly study drug related serious adverse event is unexpected or not, the apixaban, rivaroxaban or edoxaban SmPC will be used as reference safety information.

Time period for reporting AE and SAE

For each patient the standard time period for collecting and recording AE and SAEs will begin at the start of study treatment and will continue for 7 day after end-of treatment. We will proactively follow up all AEs and SAEs for each patient during the course of the study; events will be followed up to resolution, unless the event is considered to be unlikely to resolve due to the underlying disease. Every effort should be made to obtain a resolution for all events, even if the events continue after discontinuation/study completion. Mandatory reporting of new AEs ends 7 days after the end-of-treatment visit.

Recording of adverse events

If the patient has experienced adverse event(s), the investigator will record the following information in the eCRF:

- The nature of the event(s) will be described by the investigator in precise standard medical terminology (i.e. not necessarily the exact words used by the patient).
- The duration of the event will be described in terms of event onset date and event ended data.

The intensity of the adverse event will be categorised as mild / moderate / severe / life-threatening / death according to Common Terminology Criteria for Adverse Events version 4.0:

- **Mild**: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- **Moderate**: minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily life
- **Severe**: Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care activities of daily life
- Life-threatening consequences: urgent intervention indicated.

The causal relationship of the event to the study medication will be assessed as one of the following:

- **Unrelated**: There is not a temporal relationship to investigational product administration (too early, or late, or investigational product not taken), or there is a reasonable causal relationship between non-investigational product, concurrent disease, or circumstance and the AE.
- **Unlikely**: There is a temporal relationship to investigational product administration, but there is not a reasonable causal relationship between the investigational product and the AE.
- **Possible**: There is reasonable causal relationship between the investigational product and the AE. Dechallenge information is lacking or unclear.
- **Probable**: There is a reasonable causal relationship between the investigational product and the AE. The event responds to dechallenge. Rechallenge is not required.
- **Definite**: There is a reasonable causal relationship between the investigational product and the AE. Action taken: Which investigations/medical procedures/treatments that are initiated as a result of the adverse event.

The outcome of the adverse event – whether the event is resolved or still ongoing will be registred.

It is important to distinguish between seriousness and severity of AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria for SAE. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea but is not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

Reporting procedure

Adverse events, adverse events of special interest and serious adverse events

All adverse events and serious adverse events that should be reported will be recorded in the patient's eCRF. SAEs must be reported by the investigator to the sponsor, Oslo University Hospital, within 24 hours after the site has gained knowledge of the SAE. The Serious Adverse Event Report Form must be completed, documented in the eCRF, signed and sent to Øyvind H Lie. The initial report shall promptly be followed by detailed, written reports if necessary. The initial and follow-up reports shall identify the trial subjects by unique trial code numbers assigned to the latter. The sponsor keeps detailed records of all SAEs reported by the investigators and performs an evaluation with respect to seriousness, causality and expectedness.

Suspected unexpected serious adverse reactions

SUSARs will be reported to the Norwegian Medicines Agency and the local Ethics Committee. The following timelines should be followed:

The sponsor will ensure that all relevant information about suspected serious unexpected adverse reactions that are fatal or life-threatening is recorded and reported as soon as possible to the Norwegian Medicines Agency and the Regional Committee for Medical and Health Research Ethics in any case no later than seven (7) days after knowledge by the sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional eight (8) days. The sponsor shall ensure that suspected adverse reactions that are serious and unexpected are reported to the Norwegian Medicines Agency and the Regional Committee for Medical and Health Research Ethics within 15 days of the sponsor after knowledge of the event. The sponsor shall inform all investigators and involved clinicians of the trial substance in question of suspected adverse reactions that are serious and unexpected. An account of any interruption in treatment, the investigator’s assessment of the causal relationship, and consequences for further testing shall accompany the notification of suspected adverse reactions pursuant to the first and second paragraphs. SUSARs will be reported to the drug manufacturer at time of regulatory submission.

The Norwegian Medicines Agency may require that individual reports of adverse events described in collective reports should also be submitted. The sponsor shall keep detailed records of all adverse events that are reported. The records shall be submitted to the Norwegian Medicines Agency on request.

Annual safety report

Once a year throughout the clinical trial, the sponsor will provide the Norwegian Medicines Agency with an annual safety report. The format will comply with national requirements.

Clinical study report

The adverse events and serious adverse events occurring during the study will be discussed in the safety evaluation part of the Clinical Study Report.

Safety monitoring

A Data Safety Monitoring Board will be appointed to assess trial safety. The committee consist of an independent clinician and a statistician. It will receive reports summarising patient recruitment, the number of AEs / SAEs and the registered occurrence of the second co-primary endpoint (*Safety composite*) after the first 20 patients have been randomised, and once every year starting 12 months after the first 12-month control. They will be encouraged to assess signals of safety without hypothesis testing. The committee will have access to the randomisation code, and can, if they find it necessary, perform an interim analysis regarding the number of adverse events and serious adverse events. The data safety monitoring committee will receive additional information on demand and can advise temporary or permanent stop in patient enrolment. In case there is worry of a pattern of worse bleeding outcome, a recommendation to abort the study will be given to the project leader. The data safety monitoring committee is independent from the sponsor and will be composed of individuals with no competing interest with regard to the study investigational products or study outcome.

Accountability of investigational products

The batch number of every container of investigational products will be registered at every visit, both by telephone and physical visits. The batch information will be systematically stored in the eCRF, to enable secure identification of batches involved in any adverse events.

Data management and monitoring

Data will be stored and handled according to the given permissions and applicable regulations. The data will not be used for economic benefit or be made available for commercial actors.

Electronic case report forms (eCRF)

ACASA-TAVI will use an online electronic Case Report Form (eCRF) on the Viedoc platform. The designated investigator staff will enter the data required by the protocol into the eCRF. The Principal Investigator is responsible for assuring that data entered into the eCRF are complete, accurate, and that entry is performed in a timely manner. If any assessments are omitted, the reason for such omissions will be noted in the eCRFs. Corrections, with the reason for the corrections will also be recorded. After database lock, the investigator will receive a digital copy of the subject data for archiving at the investigational site.

Source data

Some data will be recorded directly into the eCRF, which, together with the patient medical record, is to be considered the source data. All data important for patient safety and continued care must be duplicated in the patient's medical record as described below. Study-specific imaging data and blood analyses are independent source data.

The medical records of each patient should clearly describe at least:

- That the patient is participating in the study
- Date when the informed consent was obtained from the patient
- Results of all assessments confirming a patient's eligibility for the study
- Diseases (past and current; both the disease studied and others, as relevant)
- Surgical history, as relevant
- Treatments withdrawn/withheld due to participation in the study
- Results of assessments performed during the study
- Treatments provided, changes in treatments during the study and the time points for the changes
- Visits to the clinic / telephone contacts during the study, including those for study purposes only
- Non-Serious Adverse Events and Serious Adverse Events (if any) including causality assessments
- Date of, and reason for, discontinuation from study treatment

- Date of, and reason for, withdrawal from study
- Date of death and cause of death, if available

Study monitoring

The investigator will be visited on a regular basis by the Clinical Study Monitor, who will check that the study is conducted as approved by the Ethics committee and adheres to GCP guidelines.

Sponsor's representatives (e.g. monitors, auditors) and/or competent authorities will be allowed access to source data for source data verification in which case a review of those parts of the hospital records relevant to the study may be required.

Trial monitoring will be performed by the Clinical Trial Unit, Oslo University Hospital.

Confidentiality

The investigator shall arrange for the secure retention of the patient identification and the code list. Patient files shall be kept for the maximum period of time permitted by each hospital. The study documentation (eCRFs, etc.) shall be retained and stored during the study and for 15 years after study closure. All information concerning the study will be stored in a safe place inaccessible to unauthorised personnel.

Database management

Data will be entered into the eCRF without delay and stored in the dedicated and secured online platform (Viedoc®). Data will be extracted from Viedoc for analysis, and the extracted data will be stored in dedicated, secure areas. Data will be stored in a de-identified manner, where each study participant is recognisable by his/her unique trial subject number. The data will be stored until Aug 31st, 2041 in compliance with local regulations, or until the patient requires that his/her data are deleted. Data in the eCRF will be handled according to GCP. Only the personnel authorised to enter and/or analyse data (i.e. investigators) will have access to the database.

Biobank

A biobank will be established at the Dept. of Cardiology, Oslo University Hospital, Rikshospitalet for the analysis of serum and plasma. The samples will be stored in multiple aliquots and labelled with the unique trial subject number, and the letter A signifying baseline, and the letter B signifying the visit at end-of-study. The samples will be stored at -80 degrees Celsius in a dedicated research freezer. The material is scheduled for destruction by Aug 31st, 2041. Dr. Øyvind H Lie at Oslo University Hospital, Rikshospitalet will be responsible for the biobank. Biochemical analyses may be

performed at other participating centres, and the samples may be shipped between countries for storage and analyses.

Data Sharing

In agreement with good research ethics, we will share anonymized data sets with the medical community via the medical journal upon submitting the manuscript.

Potential risks and benefits

There are certain potential risks associated with participation in the trial. All investigational products have potential adverse effects. The risks of bleeding seem to be balanced between the two arms, but this is also a matter of trial investigation. The risk of adverse effects like anaemia, gastro-intestinal events, skin reactions, allergic reactions and increased biochemical liver function tests also seem to be balanced between the two randomized groups. However, this has not been tested head-to-head in this population in previous trials.

Potential benefits should also be considered. If the trial hypothesis proves to be correct, half of the included patients will have access to superior treatment. Trial participants will have close contact with the TAVI performing institution and may consider it favourable to have their follow-up at a high-volume centre. The follow-up will be closer than standard clinical care.

Overall, we consider participation in ACASA-TAVI to be of relatively low risk. The balance between potential risks, benefits and clinical implications seem to justify the investigation.

Statistical methods and data analysis

Determination of sample size

Sample size estimates are calculated based on limited previous data from different populations and assumptions.

Based on previous studies, the first co-primary endpoint (HALT) can be expected to occur in approximately 20% of patients treated with ASA[12, 13]. To obtain 80% power with a two-sided 0.05 alpha for a 50% reduction in the primary efficacy endpoint in the DOAC group, 310 patients should be randomized 1:1. A 50% reduction is clinically relevant and is a realistic size based on previous indirect data[12, 13].

The estimated sample size for the second co-primary endpoint is more complex and relies on additional assumptions. There are no placebo-controlled trials of ASA after TAVI, and therefore a non-inferiority margin cannot be based on preservation of a previous effect estimate of the active comparator. The predefined non-inferiority margin was therefore based on clinical judgement and other acknowledged estimates in the field. Previous expected estimates of 1-year rate of the *Safety Composite* endpoint have been presented at 34% in the ASA-group[8] and 31% in the DOAC group[10]. The results of those trials are not suited as estimates because they studied to different population with vastly different baseline risk. We considered a non-inferiority margin of 35% relative to the active comparator to be clinically meaningful and adopted the previous estimates of event rates. This relative margin is similar to the non-inferiority margins used in previous trials involving DOAC[18, 19], and gives an absolute margin of (34 x 1.35-34) 11.9 percentage points which should not be crossed by the upper boundary of the 95% confidence interval for the rate of the *Safety composite* endpoint in the DOAC group compared to the ASA group. A one-sided 0.025 alpha requires 310 patients to be randomized 1:1 to obtain 80% power to show non-inferiority. To account for loss to follow-up and withdrawal of consent in 10-15% of participants, a total of 360 patients will be randomized to ensure power for both the co-primary endpoints (HALT, *superiority*, and Safety composite, *non-inferiority*).

We do not consider sample size estimations to be relevant for the 5- and 10-years analyses. The data will be dependent on the 12-month analysis, and the assessment will be based on these data. It is of the greatest clinical and scientific interest to assess the long-term implications of the intervention and the interaction with the 12-month first co-primary endpoint.

- *If sample sizes were to be considered*, one systematic review and meta-analysis estimated the 5-year rate of a similar endpoint at 52%[20]. A Logistic regression assessment for clinically relevant 35% reduction in the odds of the primary outcome would require a total of 256 patients randomized 1:1 for 80% power at 0.05 alpha. The same assumptions and a modest 75% 10-year incidence of the primary endpoint would require a total of 178 patients randomized 1:1 to have power for a 35% hazard reduction with the same power and alpha. Considering a diminishing alpha of 0.025 for the 5-year analysis and 0.01 for the 10-year analysis would still uphold 80% power for 35% hazard reduction well within the intended sample size of 360 patients.

With this sample size it is likely that the research question will be adequately answered.

Randomisation

Allocation- sequence generation

Balanced, permuted block randomisation (in a 1:1: ratio for the two study arms) will be performed online in Viedoc™.

Allocation- procedure to randomise a patient

We will use a computerised randomisation procedure for treatment allocation. Random treatment allocation will be executed on the online, password-protected platform designed for study purposes (Viedoc™) once eligibility has been confirmed and the informed consent has been signed.

Blinding

It is vital for an open-label blinded-endpoint randomized trial to maintain proper blinding to uphold scientific integrity of data and approximate causal inference. Therefore, careful logistic arrangements will be made to avoid bias in the endpoint adjudication. Only the investigators assessing the outcome measures will be actively blinded for the allocation

Case report form

Relevant clinical events may be registered in the electronic medical records or by direct patient interview. The clinical event adjudication committee cannot access the electronic records without being un-blinded to the randomization. Similarly, they cannot talk directly to the patients without risk of un-blinding. Therefore, case report forms (CRF) have been developed by the adjudication committee (interview guide, appendix). The clinical CRF will be filled by a research nurse or research fellow at 3, 6, 9 and 12 months by telephone interview, direct patient interview and access to the electronic medical records. The completed CRF will be made available to the endpoint adjudication committee for data entry via the eCRF. To avoid adjudication bias, the clinical endpoint adjudicator will not have access to the eCRF of the cardiac CT and echocardiographic adjudication.

Cardiac CT

Cardiac CT registrations will be de-identified, undated, and coded with the patient study ID to ensure that the reader will not come across details of the treatment. The de-identification will be performed by the coordinating investigator who will either be present at the acquisition at the core lab centre or receive transferred acquisitions from collaborating centres. Only de-identified acquisitions will be made available to the expert CT reader in the adjudication committee. Registration of structural abnormalities will be made on the CT eCRF. To avoid adjudication bias, the cardiac CT endpoint adjudicator will not have access to the eCRF of the clinical and echocardiographic adjudication.

A second expert reader will be contacted by a principal investigator if the primary reader finds:

- Blinding is compromised. The primary reader ensures proper blinding and forwards the exam for blinded analysis.
- There is uncertainty in the adjudication. Consensus will be achieved.

Echocardiography

Echocardiographic recordings will be de-identified, undated, and coded with the patient study ID using the dedicated function on the scanners. The study recordings will be performed and coded by a coordinating investigator or received from a collaborating centre and coded before it is made available to the expert cardiologist in the adjudication committee. Registration of the echocardiographic indices in question will be made on the echocardiographic eCRF. To avoid adjudication bias, the echocardiographic endpoint adjudicator will not have access to the eCRF of the clinical and cardiac CT adjudication.

A second expert reader will be contacted by a principal investigator if:

- Blinding is compromised. The primary reader ensures proper blinding and forwards the exam to a principal investigator for blinded analysis.
- There is uncertainty in the adjudication. Consensus will be achieved.

Population for Analysis

The following populations will be considered for the analyses:

- Intention to treat (ITT) population: All randomised participants, regardless of protocol adherence.
    - This population will be used do assess superiority for the first co-primary endpoint *HALT* and all non-safety secondary endpoints.
- Safety population: All patients who have been enrolled in the trial, and who have received at least one dose of the investigational medicinal product (DOAC).
    - This population will be used to assess the secondary safety endpoints.
- Per-protocol population (PP): Includes all subjects who have completed 12 months of treatment.
    - This population will be used to assess non-inferiority for the second co-primary endpoint *Safety Composite*.

Planned analyses

A separate detailed Statistics Analysis Plan (SAP) will be developed in collaboration with the dedicated study statistician employed by the Clinical Trial Unit at Oslo University Hospital before data lock.

The first main statistical analysis is planned when the last patient has completed the end-of-treatment visit 12 months after randomisation. The number and severity of adverse events will be assessed consecutively. Deviation from the original statistical plan will be described and justified in the Clinical Study Report. Amendments to plan can be done until the day of database lock.

After the first analysis, the randomization group will be removed from the CFR during the adjudication of long-term clinical endpoints. The second planned analysis is after 5 years, and the last analysis is planned after 10 years. These two will be analyses of the clinical outcome of the patients.

Statistical analysis

The preferred statistical analysis software pack of the principal investigator is Stata SE (StataCorp LLC, College Station, TX). The active available version at the time of study completion will be used. Dedicated study statistician will be employed via the Clinical Trial Unit (CTU) at Oslo University Hospital for the entire study period. The final anonymized dataset will be shared with the publishing journal to ensure transparency of the results.

Co-primary endpoints

The co-primary endpoints at 12 months will be tested using chi-square tests of proportions. The first co-primary endpoint will be tested for superiority using a two-sided chi-square test at the 0.05 significance level, and the second co-primary endpoint *Safety Composite* will be tested for non-inferiority using the computed one-sided non-inferiority limit corresponding to an upper end of the 95% confidence interval of the DOAC group 11.9% above the proportion in the ASA group.

We have not planned to test for between-group differences in baseline characteristics or to perform adjusted analyses of the co-primary endpoints. There will be no statistical correction for the use of co-primary endpoints, but study success will not be declared unless both null hypotheses are rejected.

Primary endpoint (MACE) at 5 and 10 years

The study will be re-visited after 5 and 10 years to explore the intervention effect on major adverse cardiac events/MACE (intention-to-treat and per-protocol; composite of time to stroke, myocardial

infarction, heart failure hospitalization, redo TAVI, cardiac death, type 3 or 4 bleeding defined by VARC-3). The rate of MACE at the 5- and 10-year milestones will be assessed, and the intervention effect will be assessed by rate ratios.

These two analyses will be supplemented by a competing risk-regression to account for the competing risk of non-cardiac death. We will also assess the interaction between DOAC intervention and SVD at 12 months for reduction in MACE to assess whether a possible favourable signal is mediated through SVD.

Secondary endpoint at 5 and 10 years

The rate of the individual components of MACE will be assessed, and the rate ratio will explore any effect of the intervention. The repeated echocardiographic parameters of left ventricular function and aortic valve hemodynamic performance will be entered to a linear mixed model regression to assess progression of the valve degeneration. The same will be performed for NYHA class deterioration. The randomization group will be entered to this regression as an interaction term with time to assess the effect of 12-month DOAC intervention on the development of hemodynamic valve degeneration.

Pre-defined subgroup analyses

Certain characteristics are associated with increased risk of SVD in previous reports. We trust the randomization for balanced allocation, and no stratified randomization is planned. However, interaction effects in subgroups of interest will be assessed in the primary study:

- Age <75 and ≥75 years old
- Females and males
- Diabetes mellitus
- Hypertension
- Preserved and impaired renal function
    - Estimated glomerular filtration rate cut-off <30 ml/min
- Balloon-expanded vs. self-expandable valve
- Post-dilatation vs no post-dilatation
- Supra-valvular prosthesis position
- Ascending aorta diameter > and ≤ 30 millimetres

- High and low frailty index

Key secondary endpoints

The rates of the predefined key secondary endpoints (Clinical efficacy, *Safety composite* superiority, Thromboembolic events, Bleeding events, Cardiac death) will be tested in a hierarchical order, meaning that hypothesis testing stops at the first non-significant endpoint ($p \geq 0.05$).

Secondary safety endpoints

Safety analyses will include tabulation of type and frequency of all adverse events. Any serious adverse events will be reported with comprehensive narratives. Any value of safety laboratory parameters outside normal ranges will be identified.

Exploratory secondary endpoints

The secondary endpoints that are defined as “exploratory” in the protocol will be tested and interpreted as hypothesis generating.

Missing data

Every reasonable effort will be made to minimize missing data, but it is expected that some CT-scans will be of insufficient quality and that some of these elderly patients will be unavailable for 1-year adjudication of the primary efficacy endpoint HALT. Less, but some, missing data is expected for Safety Composite. Some data may be missing completely at random (MCAR) and missing at random (MAR), but some instances of data missing not at random (MNAR) may occur if either the therapy increases likelihood of being available for 1-year analysis by improving HALT or decreases the likelihood for 1-year analysis by increasing incidence of the Safety Composite. Therefore, we will take conservative and simplistic measures to handle missing data. Missing data on the primary endpoint analysis will be replaced using hot-deck imputation using random allocation with a 5:1 ratio of failures for the first co-primary endpoint HALT and a 3:1 ratio of failures for the second co-primary endpoint Safety Composite. These ratios are based on the expected prevalence used in the sample size estimations. These imputations will be evenly distributed and therefore bias the distribution of HALT towards the null hypothesis.

Sensitivity analysis for the primary endpoints will be performed on the complete-case data and on worst-case imputation data. Additional post-hoc sensitivity analyses will be performed if unexpected patterns of missing data are observed.

Project management

Investigator delegation procedure

The principal investigator is responsible for making and updating a "delegation of tasks" listing all the involved co-workers and their role in the project. He will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved.

Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. All significant protocol deviations will be recorded and reported in the Clinical Study Report (CSR).

Study amendments

If it is necessary for the study protocol to be amended, the amendment and/or a new version of the study protocol (Amended Protocol) must be notified to and approved by the Competent Authority and the Ethics Committee according to EU and national regulations.

Audit and inspections

Authorised representatives of a Competent Authority and Ethics Committee may visit the centre to perform inspections, including source data verification. Likewise, the representatives from sponsor may visit the centre to perform an audit. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (ICH/GCP), and any applicable regulatory requirements. The principal investigator will ensure that the inspectors and auditors will be provided with access to source data/documents.

Management

The project is based in the Section of Interventional Cardiology, Oslo University Hospital.

- Principal Investigator:
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- Steering Committee
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    - Dr. Ketil Lunde, Oslo University Hospital
- Endpoint Adjudication Committee
    - Dr. Kaspar Broch, cardiologist, leader, clinical events
        - sbbrok@ous-hf.no
    - Dr. Christian H. Eek, cardiologist, valvular cardiac CT expert
    - Dr. Jan Otto Beitnes, cardiologist, echocardiography expert
- Data Safety Monitoring Board
    - Prof. Rune Wiseth, cardiologist, St. Olavs Hospital, Trondheim, Norway
        - rune.wiseth@stolav.no
    - TBD, external statistician

Ethical and regulatory requirements

The study will be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP and applicable regulatory requirements. Registration of patient data will be carried out in accordance with national personal data laws.

Ethical considerations for participants

If the hypothesis of the study is correct, half of the patients will be randomized to a superior treatment regimen without increased bleeding risk. This constitutes a significant benefit. The uncertainty regarding bleeding rates is a possible risk. Because there is no documentation of

increased bleeding risk with anticoagulation versus single platelet inhibition, we consider the intervention not to impose unjustified risk for the patients.

The active study protocol will not include study-specific invasive procedures. The additional CT assessment after 12 months will expose the patients to an additional contrast and radiation dose over the regular clinical course. However, the contrast dose is low and overt kidney damage is very uncommon after contrast-enhanced CT.

Individuals who consent to the study will commit to an additional visit at the academic institution, with travel cost and risk. They will also contribute with personal information in a registry, and thereby trust the sponsor to treat their data appropriately.

Ethics committee approval

The study protocol, including the patient information and informed consent form to be used, must be approved by the regional ethics committee before enrolment begins. The investigator is responsible for informing the regional ethics committee of any serious and unexpected adverse events and/or major amendments to the protocol as per national requirements.

Trial registration

To ensure transparency, the protocol is registered in the EudraCT database and will be registered on www.clinicaltrials.gov before inclusion of the first patient.

Informed consent procedure

The investigator is responsible for giving the patients full and adequate verbal and written information about the nature, purpose, and potential risks and benefits of the study. Study participants will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorised individuals other than their treating physician.

It will be emphasised that study participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever she/he wants. This will not prejudice the patient's subsequent care. Written informed consent must be obtained for all study participants before enrolment in the study. This will be done in accordance with the national and local regulatory requirements. The investigator is responsible for obtaining signed informed consent.

A copy of the patient information and consent form will be given to the patients. The signed and dated consent forms will be filed in the Investigator Site File binder.

Subject identification

The investigator is responsible for keeping a list of all patients (who have received study treatment or undergone any study specific procedure) including patient's date of birth and personal number, full names and last known addresses. The patients will be identified in the eCRFs by a study-specific, unique identification number.

Trial sponsorship and financing

ACASA-TAVI is an investigator-sponsored study (ISS). Funding is not finalized. We will apply for an open project support from the public research grants of South-Eastern Norway Health Authorities. We will not apply for funding from industry outside of provided tablets. The investigators take sole responsibility for the integrity of the data, the writing of the manuscript and the dissemination of the results.

Trial insurance

The Principal investigator has insurance coverage for this study through the Norwegian Pasientskadeloven. Insurance for the intervention will be obtained from Legemiddelforsikringen.

Cost-benefit considerations

The project will need considerable funding for thorough and precise execution. Any unforeseen events may also impose a cost to the public hospital system. The cost of medication is not negligible. On the other side, the potential economic benefits from reduced rate of re-intervention, frequent hospitalization and earlier death are substantial. Therefore, our general consideration is that this project holds great potential for cost benefit in intermediate and long-term.

Publication policy

Upon study completion and finalisation of the study report the results of this study will either be submitted for publication and/or posted in a publicly assessable database of clinical study results. We will allow for a separate publication of baseline characteristics once all subjects have been enrolled.

The results of this study will also be submitted to the Competent Authorities and the Regional Ethics Committees according to EU and national regulations. All personnel who have contributed significantly with the planning and performance of the study (Vancouver convention 1988) may be included in the list of authors. The funding sources have had no role in the conception of the study;

neither will they participate in the implementation of the trial, in the analyses of the results, or in the decision to publish.

Authorship

All manuscript authorships of the main analysis and spin-off projects must be according to ICMJE recommendations and must be approved by the steering committee.

Popular science dissemination

We have made arrangements with the national patient organization (LHL, Landsforeningen for Hjerte- og Lungesyke) to aid in public science dissemination at the time of the main analyses.

User representation

A panel of users has been recruited via the national patient organization (LHL, Landsforeningen for Hjerte- og Lungesyke). The user panel has participated in the trial planning. They have emphasized the importance of registering quality of life endpoints. The elements highlighted in these discussions are all captured in the KCCQ, EQ-5D-5L and HADS questionnaires (especially symptoms like breathlessness, anxiety and depression, and apathy or fatigue). Furthermore, they have been consulted in establishing the 3-month follow-up intervals during the treatment year, which is aimed at creating a compromise between good safety monitoring and individual intrusiveness. The user panel also requested routines for interaction between the study centre and the local hospitals with regards to clinical information generated from the study follow-up. The panel highlights the importance of safety during the treatment period, and have suggested that a contact person in the trial (e.g. study nurse or research fellow) will be made available for every-day questions. This person should have immediate access to trial management.

Further user representation is planned at the following time-points (all approximate):

- September 2021
    - Start-up meeting prior to enrolment of first patient, discussions of approved study proceedings and incorporations of previous feedback. Discussions of whether additional alterations should be made before inclusion starts.
- March 2022
    - Early evaluation meeting after 6 months of inclusion experience and early telephone follow-up. Discussions of challenges.
- October 2022, 2023 and 2024

- Yearly evaluations and discussions of progression and interaction with trial participants. Considerations of remarks to be made in the yearly rapport.

The user panel will receive re-imbursement for any expenses and will receive a non-monetary gratification for their efforts. The user representation panel consists of:

- Anne Grete Funderud
- Per Bøhler
- Irene Steinsvik, user representation coordinator at LHL.
    - irene.steinsvik@lhl.no (telephone 95706313)

Spin-offs

Spin-off projects are analyses planned around the primary inclusion database. Projects that are not pre-defined must be approved by the Steering Committee and Partners after written project proposal. Spin-off projects will have a dedicated supplementary protocol.

Planned spin-off analyses

- The association between structural valve degeneration/HALT at 12 months and MACE at 5 and 10 years.
- The association between repeated echocardiographic and CT indices of valve degeneration.
    - Focus on myocardial work index, register blood pressure during echo.
    - 3D volume acquisitions
- Echocardiographic predictors of adverse outcome. Assessment using dedicated comprehensive echocardiography prior to TAVI.
- Sub-group with cerebral MR performed before and 6-12 months after TAVI. Stratified random selection from both intervention arms. The effect of DOAC related to ASA for reduction of subclinical cerebral micro-emboli will be assessed, together with neurological exam and cognitive testing.
    - Primary outcome measure will be cerebral ischemic lesions using diffusion weighted imaging and mean diffusivity. Limited data exist, but one abstract suggested a remarkably high prevalence after TAVI (92% of 109 patients), mostly sub-clinical. Because most of these lesions are sub-clinical, we believe a substantial reduction

should be seen with DOAC before any clinical benefit can be hypothesized. A 50% reduction would mandate 17 patients from each intervention group for an alpha value of 0.05 and 80% power. We will include 45 patients (1 of 8 random patients from the main trial) to allow for loss to follow-up, coincidental skewed distribution between intervention groups and deviation from expected prevalence of outcome.

- Assessment of biomarkers associated with subclinical structural valve degeneration/HALT
- Standard clinical biomarkers after 3 months
- Subgroup analysis with repeated CT at 3 and 12 months to assess dynamic SVD Stage 1.
- Technical optimization of cardiac CT protocol for clinical use
- Arterial elastance as marker of biological age – invasive pressure validation and association with clinical outcome (Thomas Helle-Valle and Njord Nordstrand)
    - Ultrasound acquisition during TAVI for invasive pressure validation
- Invasive pressure assessment of aortic valve regurgitation. Datapoints are routinely assessed during the clinical procedure. We will use these to explore invasive pressure predictors of significant para-valvular regurgitation.

Partners

Partners are collaborating units with their contact person. They have key roles in the main study and can propose subsequent spin-off studies.

Section for echocardiography, Oslo University Hospital, Rikshospitalet

The section for echocardiography at the Department of Cardiology is the largest echocardiographic laboratory in Norway and has international accreditation. More than 10.000 echocardiographic exams are performed every year, including on many patients with aortic stenosis before and after TAVI. Qualified and dedicated echocardiographers and technicians contribute with acquisitions and interpretations of optimal quality.

- Helge Skulstad, MD PhD, Head of Section

The Intervention Centre, Oslo University Hospital, Rikshospitalet

The intervention centre at Oslo University Hospital has state-of-the-art hybrid operating theatres and modern CT-scanners. They have good accessibility for high-end CT and will perform spin-off efforts to optimize cardiac CT protocols, and good availability for cerebral MR.

- Ragnhild Undseth, MD PhD, Head of Radiology

Department of Internal Medicine, Sørlandet Sykehus, Arendal

The Section for Cardiology at the Department of Internal Medicine at Sørlandet Hospital, Arendal, is a key collaborator in the management of patients with aortic stenosis. They have good accessibility for repeated CT assessments, and will conduct controls and spin-off analysis with repeated CT at 3 and 12 months.

- Sverre Høie, MD, Consultant Cardiologist

Research Institute for Internal Medicine, Oslo University Hospital

The institute for research in internal medicine specialises in biomarker analyses and will be pivotal in the spin-off studies assessing markers of micro-thrombosis and heart failure.

- Thor Ueland, MD PhD, Professor

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Signature Page

I hereby declare that I will conduct the study in compliance with this protocol and the applicable regulations:

Name	Title	Role	Date	Signature
Øyvind H Lie	MD, PhD	Principal Investigator		
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